Deckblatt Telefax
Cover sheet

4718 '00 AUG 30 A9:40

Byk Gulden
Lomberg Chemische Fabrik GmbH
D-78403 Konstanz

Institut für Pathologie
und Toxikologie
Friedrich-Ebert-Damm 101
D-22047 Hamburg

Telefon (040) 69422-02
Telefax (040) 69422-188

Empfänger/Addressee	Absender/Sent by	Datum/Date
Joseph DeGeorge	Abt./Dept. FPT/Knaack	29.08.2000
Telefax 001-301-594-5147	Telefax +49/40/69422- 183 Tel./Phone +49/40/69422- 156	

Diese Mitteilung besteht aus 4 Seite(n) / This Telefax consists of 4 Page(s) ☐ Start ☐ Fortsetzung / Continued

☐ Bitte Rückruf/Please call ☐ Bitte Stellungnahme/Please comment ☐ Bitte Genehmigung/Please approve

OOD-1407

C2

1. line 7: delete "and patients"
2. line 7: delete "receiving marketed products", we actually do SP studies in order to get market authorization!
3. line 17: delete Note 1 = it is repetitous and makes sense best in Japanese draft guideline for General Pharmacology
4. line 18: delete "In the ICH non-clinical safety guidelines", text could be shorter by starting with "The term" Safety Pharmacology Studies "first appeared in the ICH topics etc.. This is shorter .
5. line 23+24: unnecessary
6. line 43-46: not very clear replace 40-46 by following text:
   Certain safety pharmacology endpoints may not need to be generated in separate safety pharmacology studies if they have been or can be incorporated in the design of other studies (eg. toxicology, kinetic studies). It must be recognized, however, that dedicated safety pharmacology studies may have an increased sensitivity for detecting adverse effects in comparison to studies used to detect overt toxicity in conventional animal toxicity studies.
7. line 51: Note 2 should be part of the main text . This clear definition is very important to differentiate SP from the other studies. The terms "Prim. "or" Sec." appear often in the later text (see line 56)
8. line 53: delete "For the purpose of this document"
9. line 55: add: to exposure "in the therapeutic range and above"
10. line 84: modify in " that warrant further (investigation to establish and characterize) assessment regarding their relevance to potential etc.
11. line 88: what is " a more general screening approach ", this needs clear definition.
12. line 94: Add after "studies" the sentence "These functions are called vital functions". Otherwise line 98 is not clear .
13. line 121: delete "on vital functions", because not only core package, but all possible studies are most probably meant .
14. line 121-127: the current wording to request conscious animal studies is too strong. Replace test by the following:
    In conducting in vivo studies on vital functions either anesthetized or conscious animal models my be used. It is preferable to use unanesthetized animals that are unrestrained using telemetry or other suitable instrumentation methods. Data from animals conditioned to the laboratory environment are preferable to data coming from restrained or unconditioned animals. In the use of unanesthetized animals the avoidance of discomfort or pain is a foremost consideration.
15. line 126+127: plus compare to recording in line 155-158
    We would point out the likely conflict between the statement on avoiding discomfort in conscious animals (see line 126+17) and the dose-selection issue (see line 155-158). Pushing the dose to extreme levels in order to "see something" will certainly lead to nonspecific intolerability and discomfort to the conscious animals in many cases. We can't have it both ways:

16. line 130: please define "adequate "
17. line 131: delete "or absence"
because demonstration of the absence of an effect is not feasible.
18. line 129-136: Suggested rewording:
The number of animals or isolated preparations should be adequate to clearly demonstrate an effect of the test substance. This should take into consideration the size of the physiologically relevant effect together with the variability of the test system. Appropriate negative and positive controls groups should be included in the experimental design but in well characterized test systems **(note: I've intentionally omitted in vivo)** new positive controls may not be necessary for each study. The exclusion of controls from studies should be justifies.
19. line 140: delete " at least "
20. line 147 there have been many comments on 2.4.1. The most comprehensive one is the following:
In vivo studies
This is a difficult section. One problem is that various types of studies are being lumped together. The dose selection may be different for screening type studies versus studies where an effect is known to be present. I think the common feature of all is that there should be a rational justification of the dose selection.
Suggested rewording: of line 148-162
Safety pharmacology studies should be designed to define the dose-response curve of a given adverse effect, if an effect is present. Furthermore, the time course (e.g. onset and duration of the effect) of the effect should be defined when feasible. The dose-response for the adverse effect should be compared to the dose-response of the primary pharmacodynamic effect in the test species used or compared to the therapeutic effect in humans, if this information is available.
It is recognized that there are potential species differences in both the adverse effect dose-response as well as in the primary pharmacodynamic effect dose-response. Furthermore, it is recognized that drug exposure in patients may inadvertently in certain cases greatly exceed the exposure produced by the recommended therapeutic dose. Therefore, doses used in safety pharmacology studies should include and exceed the primary pharmacodynamic of therapeutic range. Dose selection should be justified for each study. It is recognized that in the absence of an adverse effect the selection of the highest dose to be tested becomes somewhat arbitrary but could be based on: physico-chemical limitations of the test substance (e.g. limited solubility or bioavailability), doses leading to adverse effects or toxicity in other models or a predefine highest dose that represents a sufficient safety for a given test substance and intended clinical indication. In practice, some effects in the toxic range (e.g. tremors or fasciculations during ECG recording) may confound the interpretation of safety pharmacology effects and may also limit dose levels
21. line 148: replace " to define " by " to establish " . We want to get an idea , but super-precision is not necessary
22. line 150: replace " investigated " by " outlined " Same reason as for line 148

23. line 158: change into : in other studies of similar route and duration .(e.g. toxicology study) Explanation : One uses information from repeat dose study .
24. line 162+163: delete sentence , because confusing
25. line 162-163: delete sentence. There is no option for such a design.
26. line 164-167: replace test by the following:
    In vitro studies should be designed to establish a concentration-effect relationship, if an effect is present. A range of concentrations should be explored in order to increase the likelihood of detecting an effect on the test system. It is recognized that in many in vitro test systems nonspecific effects may emerge as the concentration is increased. Therefore, in addition to physicochemical characteristics which may limit the concentrations acheivable in a given test system, the occurrence of known nonspecific effects may form the basis for defining the highest concentration to be tested in a given in vitro test system.

    Reasoning for above text:
    Here one is thinking of HERG channel tests, for example. If it is generally accepted that most compounds will starting interacting with HERG at concentrations of approximately 10 µM and higher, why include these concentrations in your study design? In other words, if an effect at concentrations are considered to have no relevance at the onset, why generate the data?
27. line 167: change in : increase the likelyhood of detecting an effects on the test system
28. line 170: add after "non-clinical studies" "or when parmacodynamic effects require a certain period" and continue with the original test: or human use give rise .....
29. line 171-173: repeat dosing in the duration of the safety pharmacology studies should be considered to adress these effects should be rationally based
30. line 175-177: Generally , any parent compound and its major metabolite(s) with potential that achieve systemic exposure or are expected to reach the systemic ciculation in humans should be evaluated in.....
31. line 178: delete " such " .

From: JOAN CYHAN (302)892-7482
DUPONT PHARMACEUTICALS
974 CENTRE ROAD
CHESTNUT RUN PLAZA, MR2137
WILMINGTON, DE, 19805

SHIPPER'S FEDEX ACCOUNT #

FedEx.

To: Dockets Management Branch (HFA-305) (301)443-9285
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD, 20852

SHIP DATE: 29AUG00
WEIGHT: 1 LBS

Ref:

DELIVERY ADDRESS
TRK # 7903 4620 1341 FORM 0201

STANDARD OVERNIGHT

WED
AA
Deliver by:
30AUG00

20852-MD-US

IAD
ZM GAIA